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A Convenient Synthesis of (±)-3-Methoxybenzodioxane-4,9,9′-triol Neolignan, and Methyl Ethers of Isoamericanol A and Isoamericanin A†

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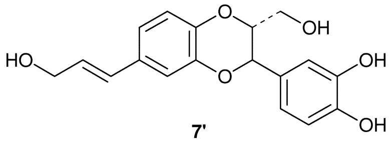
The (±)-3-methoxybenzodioxane-4,9,9′-triol neolignan **9**, and methyl ethers of isoamericanol A **8** and isoamericanin A **7** were synthesized from the readily available materials caffeic acid and ferulic acid, using a coupling reaction as a key step.

Isoamericanol A, isoamericanin A and (±)-3-methoxybenzodioxane-4,9,9′-triol neolignan are three neolignans isolated from *phytocaccaceae* and *Juniperns chinesis*[1,2] and were assigned structure **7′**, **8′** and **9** respectively through spectral studies. In the literature it is reported that natural products containing the 1,4-benzodioxane ring have cytotoxic and hepatoprotective,[3] and other biological activity associated with the 1,4-benzodioxane group,[4] but no syntheses of these particular natural products have been reported.



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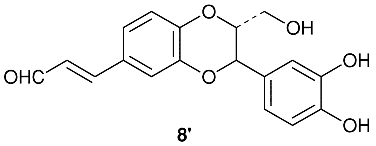

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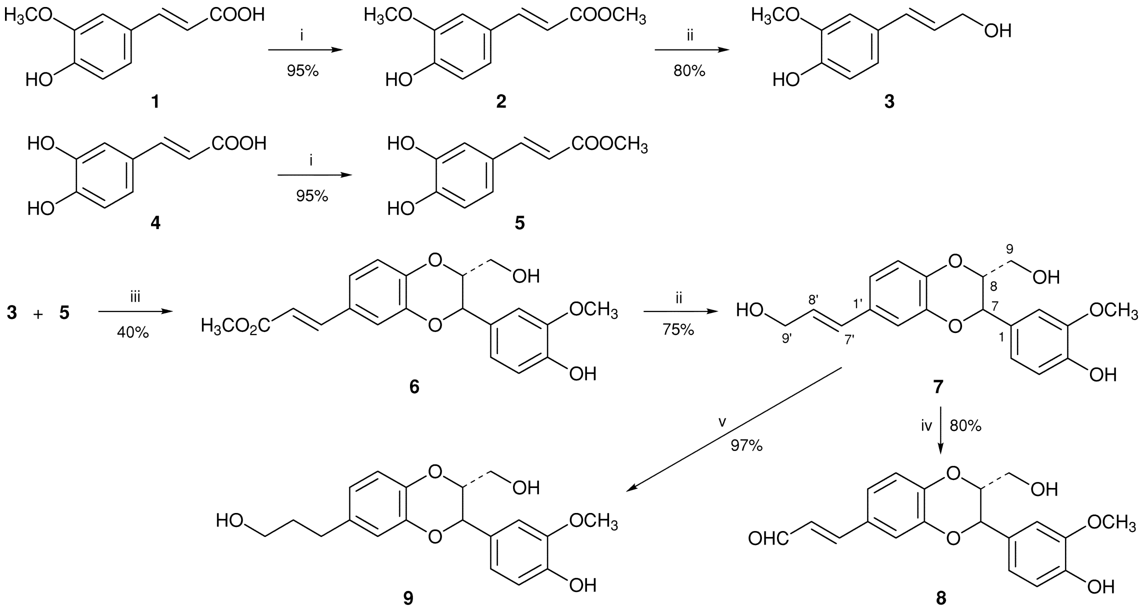
In order to study methods of construction of the 1,4-benzodioxane ring and the structure–activity relationship, we developed a facile synthetic route to (±)-3-methoxybenzodioxane-4,9,9′-triol neolignan **9**, and methyl ethers of isoamericanol A **7** and isoamericanin A **8**, in which use of silver carbonate as the oxidizing agent resulted in higher regioselectivity (*ca.* 30:1) than that obtained with silver oxide (*ca.* 20:1) by Merlini *et al.*[5]

As shown in Scheme 1, 3-(3,4-dihydroxy)phenylprop-2-enoate **5** and ferulic alcohol **3** were synthesized from the starting materials caffeic acid and ferulic acid based on an earlier report,[3] then compounds **3** and **5** were converted into key intermediate **6** by a coupling reaction, which was then reduced with $LiAlH_4$–$AlCl_3$ (3:1) to afford alcohol **7**. Then **7** was hydrogenated to get the target compound **9** and was oxidized with MnO_2–SiO_2 to obtain compound **8**.

Experimental

Melting points were measured on a Kofler apparatus and were uncorrected. Mass spectra were recorded on a ZAB-HS spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 instrument. IR spectra were recorded on a Nicolet 170 SXFT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Ac-80 and AM-400 instrument. Chemical shifts are referenced to Me_4Si on the δ scale. *J* values are in Hz. Standard flash chromatography was employed to purify the crude reaction mixture using *ca.* 200 ~ 300 mesh silica gel under positive nitrogen pressure.



Scheme 1 *Reagents and conditions*: i: CH_3OH, H_2SO_4, reflux; ii; $LiAlH_4$, $AlCl_3$ room temp.; iii, Ag_2CO_3, acetone–benzene (1:2), room temp.; iv, MnO_2–SiO_2, CH_2Cl_2 room temp.; v: H_2, Pd/C (10%)

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Methyl (E)-3-[2-*Hydroxymethyl*-3-(4-*hydroxy*-3-*methoxyphenyl*)-1,4-*benzodioxan*-6-*yl*] *propenoate* **6**.—Silver carbonate (270 mg) was added to a solution of 190 mg of methyl 3-(3,4-dihydroxy)phenylprop-2-enoate **5** and 180 mg of ferulic alcohol **3** in acetone–benzene (1 : 2; 50 ml; the mixture was stirred for 20 h at room temperature, filtered through silica gel, the solvent evaporated in vacuum and the residue flash chromatographed using light petroleum and ethyl acetate (2:1, v/v) as eluent to afford **6** as a white powder, 150 mg, yield 40%, Mp 135–137 °C. δ_H (400 MHz, [$^2H_6$]acetone); 3.50 and 3.77 (dd, 2H, *J* 12, 4, H-9), 3.70 (s, 3H, OCH_3), 3.84 (s, 3H, $COOCH_3$), 4.30 (m, 1H, H-8), 4.98 (d, 1H, *J* 8, H-7), 6.40 (d, 1H, *J* 16, H-7′), 6.65–6.96 (m, 3H, Ar-H), 7.58 (d, 1H, *J* 16, H-8′); MS, *m*/*z*: 372 (M^+, 100), 354 (69), 205 (25), 137 (46), 124 (22).

Methyl Ether of Isoamericanol A **7**.—Compound **6** (600 mg in 30 ml of THF) was added to a solution of stirred $LiAlH_4$ (200 mg) and $AlCl_3$ 9220 mg) in 40 ml of diethyl ether. The mixture was stirred at room temperature for 2 h, then saturated NH_4Cl was added, and the mixture stirred, extracted with ethyl acetate and dried, the solvent was evaporated off and the crude product was purified by flash chromatography using light petroleum and ethyl acetate (2 : 1, v/v) as eluent to give a white powder of **7** (416 mg, 75% yield), Mp 171–172 °C. Elemental analysis: $C_{19}H_{20}O_6$ requires C, 66.27, H, 5.85. Found C, 66.7, H, 5.9%. δ_H (400 MHz, CD_3CN):3.38 and 3.57 (dd, 2H, *J* 12.4, 5.1, H-9), 3.60 (s, 3H, OCH_3), 4.10 (m, 2H, *J* 5.4, H-9′), 4.30 (m, 1H, *J* 8, 5.1, H-8), 4.87 (d, 1H, *J* 8, H-7), 6.20 (m, 1H, *J* 16, H-8′), 6.46 (d, 1H, *J* 16, H-7′), 6.80–7.20 (m, 6H, Ar-H); MS, *m*/*z*: 344 (M^+, 44), 326 (80), 180 (60), 162 (73), 137 (100), 124 (60).

Methyl Ether of Isoamericanin A **8**.—To a solution of 70 mg of **7** in 50 ml diethyl ether was added activated MnO_2–SiO_2 (m/m 1:1); 600 mg; the mixture was stirred at room temperature for 24 h and filtered through silica gel, the crude product was purified by flash chromatography using light petroleum and ethyl acetate (2:1, v/v) as eluent to obtain **8** (55 mg) in 80% yield, Mp 165–167 °C. Elemental analysis: $C_{19}H_{18}O_8$ requires C, 66.66, H, 5.30. Found C, 66.5, H, 5.3%. ν/cm^{-1} (KBr): 3375, 2924, 2852, 1697, 1661, 1609, 1578; δ_H (400 MHz, [$^2H_6$]acetone): 3.38 and 3.60 (dd, 2H, *J* 12.3, 5.0, H-9), 3.74 (s, 3H, OCH_3), 4.04 (m, 1H, H-7), 4.92 (d, 1H, *J* 8, H-8), 4.11 (d, 1H, *J* 16, H-7′), 7.48 (d, 1H, *J* 16, H-8′), 6.80–7.22 (m, 6H, Ar-H), 9.53 (d, 1H, *J* 7.6, CHO); MS, *m*/*z*: 342 (M^+, 100), 324 (45), 137 (30), 124 (20).

(±)-3-*Methoxybenzodioxane*-4,9,9′-*triol Neolignan* **9**.—A solution of **8** (30 mg) in methanol (30 ml) was hydrogenated over 10% Pd/C (5 mg) under H_2 for 40 min. Then the reaction mixture was filtered through silica gel and preparative TLC afforded **9** as a colorless oil, 29 mg, 97% yield; δ_H (400 MHz, [$^2H_6$]acetone): 1.78 (m, 2H, H-8′), 2.58 (t, 2H, *J* 7.7, H-9′), 3.47 and 3.69 (dd, 1H, *J* 12, 4, H-9), 3.55 (t, 2H, *J* 6.5, H-7′), 3.85 (s, SH, OCH_3), 4.00 (m, 1H, H-8), 4.86 (d, 1H, *J* 8, H-7), 6.69–6.98 (m, 6H, Ar-H); MS, *m*/*z*: 346 (M^+, 89), 328 (55), 180 (69), 166 (72), 137 (100), 123 (40).

All the spectral data were in good agreement with those reported.[2]

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